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Novel 1,2-Disubstituted Benzimidazole Derivatives: Synthesis and *in silico* Antibacterial Activity

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A series of 14 novel 1,2-disubstituted benzimidazole derivatives was synthesized by reacting substituted benzimidazoles with ethyl succinyl chloride and characterized by spectroscopic techniques (FTIR, ^{1}H NMR and Mass). The molecular docking analyses with AutoDock Tools-1.5.7 were used to examine the interactions between the compounds and the active site residues of Topoisomerase-II enzyme (PDB ID: 1JIJ). Amongst the 14 derivatives, 11 derivatives had shown greater binding affinity with the receptor in comparison with standard drug pefloxacin.

Keywords: Benzimidazole, Molecular docking, Antibacterial, Topoisomerase-II, Binding affinity.

INTRODUCTION

Benzimidazole serves as a key component in pharmaceutical studies due to its strong affinity for various enzymatic and protein binding sites [1]. Numerous derivatives, particularly 1,2-disubstituted benzimidazoles, have demonstrated promising biological efficacies that may result in novel therapeutic applications [2,3]. The fact that compounds containing benzimidazoles are widely found in molecules that show significant activity against a variety of infections, including HIV [4], herpes [5], bacterial [6] and fungal infections [7], has sparked interest in these structures [8]. Moreover, benzimidazole derivatives have therapeutic applications like antihypertensive [9], anticonvulsant [10], analgesic [11] and anti-inflammatory [12], antidiabetic [13], anticancer [14] and antiulcer [15].

Drug research continues to benefit from the use of computer aided drug design (CADD), which reduces the time and expense associated with discovering novel targets for drugs [16]. Molecular docking, one of the CADD techniques, has been used to forecast the bioactivity of compounds using mathematical equations and to determine the binding affinities of ligands with certain targets [17]. Enzyme, known as bacterial topoisomerases-II or DNA gyrase, is vital for several fundamental biological functions, such as DNA replication and modification of DNA topology [18]. The current work is committed to synthesize new 1,2-disubstituted benzimidazole derivatives, their effectiveness and target interactions in the Topoisomerase -II receptor's active region (PDB ID: 1JIJ) are being investigated by molecular docking.

EXPERIMENTAL

The chemicals and solvents used in the synthesis were procured from different commerical suppliers and were used without any purification. Melting points of the synthesized compounds were recorded by VEEGO melting point apparatus and reported uncorrected. FTIR spectra were captured using Agilent Cary 630 FTIR in KBr method. ^{1}H NMR were obtained from Benchtop NMR Spectrometer (DRX-300) using DMSO as a solvent. Mass spectra were recorded on TSQ quantum access max triple quadrupole mass spectrometer.

General procedure for synthesis of 2-(2,3,4-substituted)-benzimidazole: In a 100 mL round bottom flask fitted with a magnetic stirrer, combine substituted *o*-phenylene diamine (1.0 mmol) and substituted benzaldehyde (1.0 mmol) and dissolved in 30 mL acetonitrile with continuous stirring at room temperature. Then added aqueous 30% H_2O_2 (36.36 mL) and aqueous

37% HCl (11.61 mL). The reaction mixture was stirred continuously at room temperature for 40 min based on the completion of reaction (indicated by single-spot on TLC; mobile phase-*n*-hexane:ethyl acetate, 7:3). After completion, the content was poured in ice-cold water (50 mL), extract the content four times with ethyl acetate and the organic layer was dried over $MgSO_4$, while ethyl acetate was evaporated using rotary evaporator. Finally the product was dried at room temperature and recrystallized with alcohol (**Scheme-I**).

General procedure for synthesis of 1,2-disubstituted benzimidazole (1C-11C): In a 250 mL round bottom flask, 1.0 mmol of 2-(2,3,4-substituted)benzimidazole and K_2CO_3 (1.0 mmol) were dissolved in 30 mL acetonitrile with continuous stirring at room temperature. Added ethyl succinyl chloride (1.0 mmol) while stirring at room temperature for 0.5 h at 60 °C. After monitoring by TLC, pour the content into 50 mL ice cold water and extracted the content with ethyl acetate and finally evaporate the organic layer with rotary evaporator. The product was dried at room temperature and recrystallized with alcohol (**Scheme-I**).

Ethyl-4-(2-(4-hydroxyphenyl)-1*H*-benzo[*d*]imidazol-1-yl)-4-oxobutanoate (1C): Colour: black; m.p.: 393-395 °C; R_f value: 0.58; yield: 74%; FTIR (KBr, ν_{max}, cm^{-1}): 3060.1 (C-OH *str.*), 2981.9, 2937.1 (C-H *str.*), 1722 (C=O *str.*), 1606.4 (C=N *str.*), 1021.21 (C-O-C *str.*); ^{1}H NMR (DMSO) δ ppm: 6.88-7.91 (m, 8H, Ar-H), 9.52 (s, 1H, Ar-OH), 3.84 (m, 2H, O-CH_2), 1.02 (t, 3H, -CH_3), 2.56 (t, 2H, CO-CH_2), 2.74 (t, 2H, CO-CH_2); Mass (m.f.: $C_{19}H_{18}N_2O_4$; m.w.: 338.36): *m/z* 338 [M^++1].

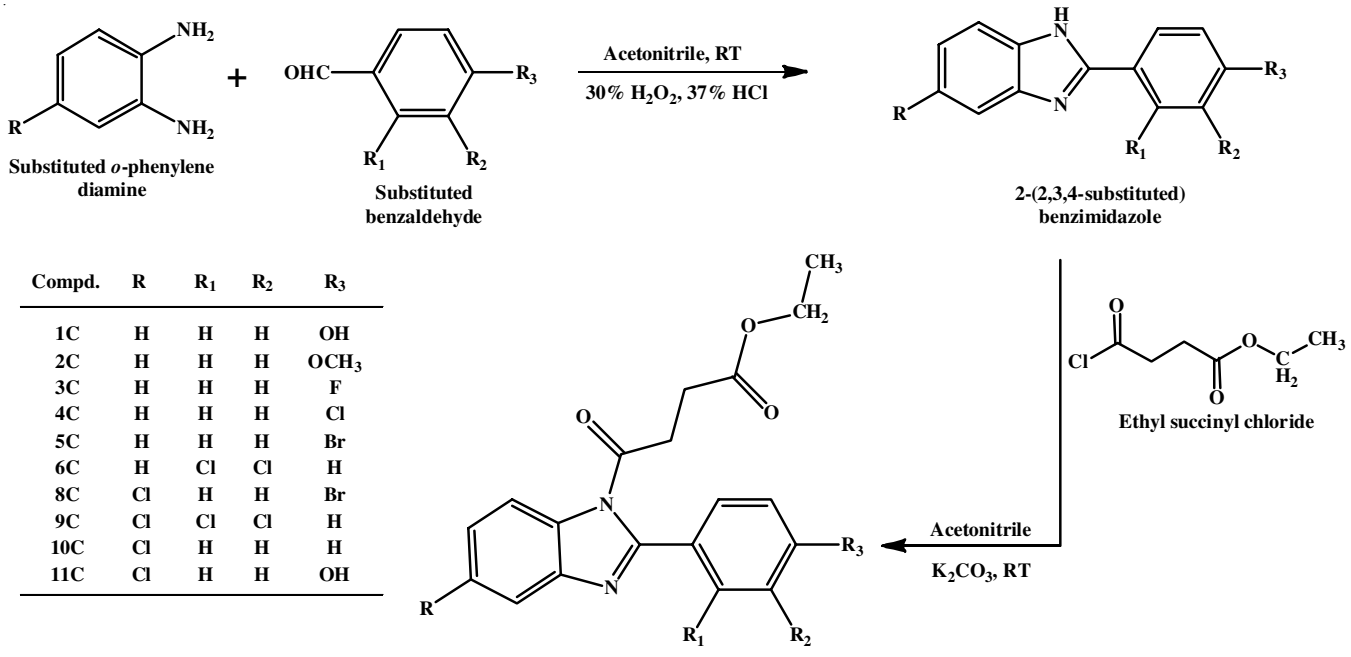
Ethyl-4-(2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazol-1-yl)-4-oxobutanoate (2C): Colour: black; m.p.: 376-378 °C; R_f value: 0.62; yield: 78%; FTIR (KBr, ν_{max}, cm^{-1}): 3060.1 (C-H *str.*), 2937.1, 2840.2 (C-H *str.*), 1722 (C=O *str.*), 1606.5 (C=N *str.*), 1025.0 (C-O-C *str.*); ^{1}H NMR (DMSO) δ ppm: 6.90-8.12 (m, 8H, Ar-H), 3.79 (s, 3H, Ar-OCH_3), 3.92 (m, 2H, O-CH_2), 1.04 (t, 3H, -CH_3), 2.61 (t, 2H, CO-CH_2), 2.78 (t, 2H, CO-CH_2); Mass (m.f.: $C_{20}H_{20}N_2O_4$; m.w.: 352.39): *m/z* 352 [M^++1].

Ethyl-4-(2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-4-oxobutanoate (3C): Colour: black; m.p.: 340-342 °C; R_f value: 0.52; yield: 79%; FTIR (KBr, ν_{max}, cm^{-1}): 2981.9 (C-H *str.*), 1722.0 (C=O *str.*), 1599.0 (C=N *str.*), 1222.6 (C-F *str.*), 1099.6 (C-O-C *str.*); ^{1}H NMR (DMSO) δ ppm: 7.05-7.63 (m, 8H, Ar-H), 4.08 (m, 2H, O-CH_2), 1.21 (t, 3H, -CH_3), 2.59 (t, 2H, CO-CH_2), 2.85 (t, 2H, CO-CH_2); Mass (m.f.: $C_{19}H_{17}N_2O_3F$; m.w.: 340.35): *m/z* 340 [M^++1].

Ethyl-4-(2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-4-oxobutanoate (4C): Colour: brown; m.p.: 373-375 °C; R_f value: 0.63; yield: 56%; FTIR (KBr, ν_{max}, cm^{-1}): 2873.7 (C-H *str.*), 1722.0 (C=O *str.*), 1677.3 (C=N *str.*), 1088.4 (C-O-C *str.*), 764.1 (C-Cl *str.*); ^{1}H NMR (DMSO) δ ppm: 7.18-8.00 (m, 8H, Ar-H), 4.03 (m, 2H, O-CH_2), 1.08 (t, 3H, -CH_3), 2.62 (t, 2H, CO-CH_2), 2.76 (t, 2H, CO-CH_2); Mass (m.f.: $C_{19}H_{17}N_2O_3Cl$; m.w.: 356.81): *m/z* 356 [M^++1].

Ethyl-4-(2-(4-bromophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-4-oxobutanoate (5C): Colour: brown; m.p.: 373-375 °C; R_f value: 0.64; yield: 54%; FTIR (KBr, ν_{max}, cm^{-1}): 2981.8, 2743.3 (C-H *str.*), 1722.0 (C=O *str.*), 1587.8 (C=N *str.*), 1010.1 (C-O-C *str.*), 682.1 (C-Br *str.*); ^{1}H NMR (DMSO) δ ppm: 7.20-7.62 (m, 8H, Ar-H), 4.05 (m, 2H, O-CH_2), 1.10 (t, 3H, -CH_3), 2.57 (t, 2H, CO-CH_2), 2.81 (t, 2H, CO-CH_2); Mass (m.f.: $C_{19}H_{17}N_2O_3Br$; m.w.: 401.26): *m/z* 402 [M^++1].

Ethyl-4-(2-(2,3-dichlorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-4-oxobutanoate (6C): Colour: red; m.p.: 415-417 °C; R_f value: 0.66; yield: 87%; FTIR (KBr, ν_{max}, cm^{-1}): 2840.2 (C-H *str.*), 1722.0 (C=O *str.*), 1423.8 (C=N *str.*), 1051.1 (C-O-C *str.*), 790.2, 738.0 (C-Cl *str.*); ^{1}H NMR (DMSO) δ ppm: 7.19-7.81 (m, 7H, Ar-H), 4.01 (m, 2H, O-CH_2), 1.08 (t, 3H, -CH_3), 2.65 (t, 2H, CO-CH_2), 2.78 (t, 2H, CO-CH_2); Mass (m.f.: $C_{19}H_{16}N_2O_3Cl_2$; m.w.: 391.25): *m/z* 391 [M^+].



Compd.	R	R_1	R_2	R_3
1C	H	H	H	OH
2C	H	H	H	OCH_3
3C	H	H	H	F
4C	H	H	H	Cl
5C	H	H	H	Br
6C	H	Cl	Cl	H
8C	Cl	H	H	Br
9C	Cl	Cl	Cl	H
10C	Cl	H	H	H
11C	Cl	H	H	OH

Scheme-I: Synthetic route of 1,2-disubstituted benzimidazoles

Ethyl-4-(2-(4-bromophenyl)-5-chloro-1*H*-benzo[*d*]-imidazol-1-yl)-4-oxobutanoate(8C): Colour: Brown; m.p.: 445-447 °C; R_f value: 0.70; yield: 78%; FTIR (KBr, ν_{max}, cm^{-1}): 2978.1 (C-H *str.*), 1707.1 (C=O *str.*), 1438.7 (C=N *str.*), 1058.5 (C-O-C *str.*), 797.6 (C-Cl *str.*), 682.1 (C-Br *str.*); ^{1}H NMR (DMSO) δ ppm: 7.10-8.32 (m, 7H, Ar-H), 4.09 (m, 2H, O-CH_2), 1.04 (t, 3H, -CH_3), 2.57 (t, 2H, CO-CH_2), 2.91 (t, 2H, CO-CH_2); Mass (m.f.: $C_{19}H_{16}N_2O_3ClBr$; m.w.: 435.70): *m/z* 435 [M^+].

Ethyl-4-(5-chloro-2-(2,3-dichlorophenyl)-1*H*-benzo-[*d*]imidazol-1-yl)-4-oxobutanoate (9C): Colour: light brown; m.p.: 337-375 °C; R_f value: 0.66; yield: 67%; FTIR (KBr, ν_{max}, cm^{-1}): 3071.3, 3034.0 (C-H *str.*), 1733.2 (C=O *str.*), 1416.3 (C=N *str.*), 1.54.8 (C-O-C *str.*), 790.2, 708.1 (C-Cl *str.*); ^{1}H NMR (DMSO) δ ppm: 7.24-8.38 (m, 6H, Ar-H), 4.05 (m, 2H, O-CH_2), 1.08 (t, 3H, -CH_3), 2.63 (t, 2H, CO-CH_2), 2.74 (t, 2H, CO-CH_2); Mass (m.f.: $C_{19}H_{15}N_2O_3Cl_3$; m.w.: 356.81): *m/z* 356 [M^+].

Ethyl-4-(5-chloro-2-phenyl-1*H*-benzo[*d*]imidazol-1-yl) -4-oxobutanoate (10C): Colour: brown; m.p.: 485-487 °C; R_f value: 0.71; yield: 72%; FTIR (KBr, ν_{max}, cm^{-1}): 2877.5, 2836.5 (C-H *str.*), 1729.4 (C=O *str.*), 1464.8 (C=N *str.*), 1051.1 (C-O-C *str.*), 790.2, 738.0 (C-Cl *str.*); ^{1}H NMR (DMSO) δ ppm: 7.43-8.29 (m, 8H, Ar-H), 4.03 (m, 2H, O-CH_2), 1.00 (t, 3H, -CH_3), 2.66 (t, 2H, CO-CH_2), 2.78 (t, 2H, CO-CH_2); Mass (m.f.: $C_{19}H_{17}N_2O_3Cl$; m.w.: 372.81): *m/z* 372 [M^+].

Ethyl-4-(5-chloro-2-(4-hydroxyphenyl)-1*H*-benzo[*d*]-imidazol-1-yl)-4-oxobutanoate(11C): Colour: brown; m.p.: 458-460 °C; R_f value: 0.72; yield: 70%; FTIR (KBr, ν_{max}, cm^{-1}): 3324.7 (O-H *str.*), 2840.2 (C-H *str.*), 1714.5 (C=O *str.*), 1412.6 (C=N *str.*), 1058.5 (C-O-C *str.*), 793.9 (C-Cl *str.*); ^{1}H NMR (DMSO) δ ppm: 6.84-8.39 (m, 8H, Ar-H), 9.61 (s, 1H, Ar-OH), 4.10 (m, 2H, O-CH_2), 1.09 (t, 3H, -CH_3), 2.59 (t, 2H, CO-CH_2), 2.73 (t, 2H, CO-CH_2); Mass (m.f.: $C_{19}H_{18}N_2O_4Cl$; m.w.: 425.69): *m/z* 425 [M^+].

In silico studies

Docking studies: The Chem-Draw professional 16.0 and chem3D Ultra software were used to draw 2D and 3D structures of the ligands. Docking evaluation was done by using Auto-Dock-Tools-1.5.7 as well as Discovery Studio 2017 R2 Client.

Preparations of protein structure: Topoisomerase-II enzyme (PDB code: 6JIJ) was selected and downloaded from the protein data bank (https://www.rcsb.org). Before employing the downloaded protein in docking experiments, it needs to be changed since it might include heavy ions, additional chains of metal ions or a co-crystallized ligand. In the Discovery Studio 2017 R2 Client, alter the protein structure by ligand molecule and water molecules, introducing polar hydrogen and preserving the protein in .pdb format.

Building of ligand structure: Chem-Draw Professional 16.0 was utilized to illustrate the structures of the synthesized benzimidazoles. The docked molecule needs to match the real ligand structures exactly as they would appear in a protein-ligand interaction. The ligands were arranged in three dimensions using the Chem3D Ultra software and their combined energy (MM2) is minimized to the lowest feasible value [19]. Each unique pdb file contains the structure of every ligand.

RESULTS AND DISCUSSION

As shown in **Scheme-I**, substituted *o*-phenylene diamines served as the starting point for the two-step synthesis that produced novel 1,2-disubstituted benzimidazoles (**1C**-**11C**). Seven different substituted benzaldehydes were reacted with substituted *o*-phenylene diamines in the presence of 30% H_2O_2 and 37% HCl using acetonitrile to yield 2-(2,3,4-substituted) benzimidazoles. Further, 2-(2,3,4-substituted) benzimidazoles were condensed with ethyl succinyl chloride in the presence of K_2CO_3 using acetonitrile at room temperature and respective 1,2-disubstituted benzimidazoles were obtained in 51-79% yield. The structures of synthesized compounds were verified by FTIR, ^{1}H NMR and mass spectroscopic analysis data. The FTIR spectra showed the C=O group stretching, C-O-C stretching, C=N stretching and carbon-halogen stretching. The ^{1}H NMR data of all synthesized compounds showed the multiple at δ 6.5-8.2 ppm, which are the characteristics of aromatic ring protons of benzimidazole ring protons and benzene ring protons. Methylene and methyl protons of the side chain at N-1 of benzimidazole were shown triplet and multiples in the range of δ 1.0-4.2 ppm. Mass spectra of the compounds showed M^+ and M^{+1} peaks of parent compounds.

Molecular docking studies: Molecular docking method was utilized to investigated the mechanism by which the novel pharmacological entity interacts to the Topoisomerase-II enzyme (PDB ID: 1JIJ) to exhibit its antibacterial properties [20]. The evaluation of docking was conducted using Discovery Studio 2017 R2 Client in conjunction with AutoDockTools-1.5.7 [21]. Newly synthesized benzimidazoles were docked with Topoisomerase-II (PDB ID: 1JIJ). The AutoDock program was used to carry out all required adjustments, including the removal of water, the addition of polar hydrogen, the Kollman charges and the assignment of AD4-type atoms. The grid box for blind docking should now be created with the following dimensions: x = 48, y = 70 and z = 56; the center grid box's spacing should be x = -11.687, y = 17.275 and z = 91.74. The spacing (Å) should be 1.000. Potential interactions between ligand proteins were examined using the software discovery studio, which also allowed for the saving of 2D ligand interaction schematics.

Pefloxacin has been chosen as the standard drug due to its ability to inhibit bacterial Topoisomerase-II. Table-1 listed the binding affinities of all the synthesized benzimidazoles together with pefloxacin, which demonstrated a good docking score and contact with important residues of amino acids within the receptor's binding pocket. The results showed that compound **9C** have a maximum affinity of -9.2 Kcal/mol in virtue of the higher number of interactions (Asp A:40, Lys A:84, His A:50, Gly A:193, Leu A:70, Tyr A:36, Arg A:88) with the protein and includes hydrogen bond. A slightly lower binding affinity was shown by compound **8C** equals -9.1. Effective binding affinities of -8.9 Kcal/mol were also demonstrated by compounds **1C**, **2C**, **10C** and **11C**, whereas compounds **3C**, **4C**, **6C**, **7C**, **13C** and **14C** showed binding affinities between -8.1 and -8.8 Kcal/mol. The minimal binding affinities of compounds **5C** and **6C** were found to be -6.6 and -6.9 Kcal/mol, respectively. Analyzing the binding affinities, all the synthesized benzimi-

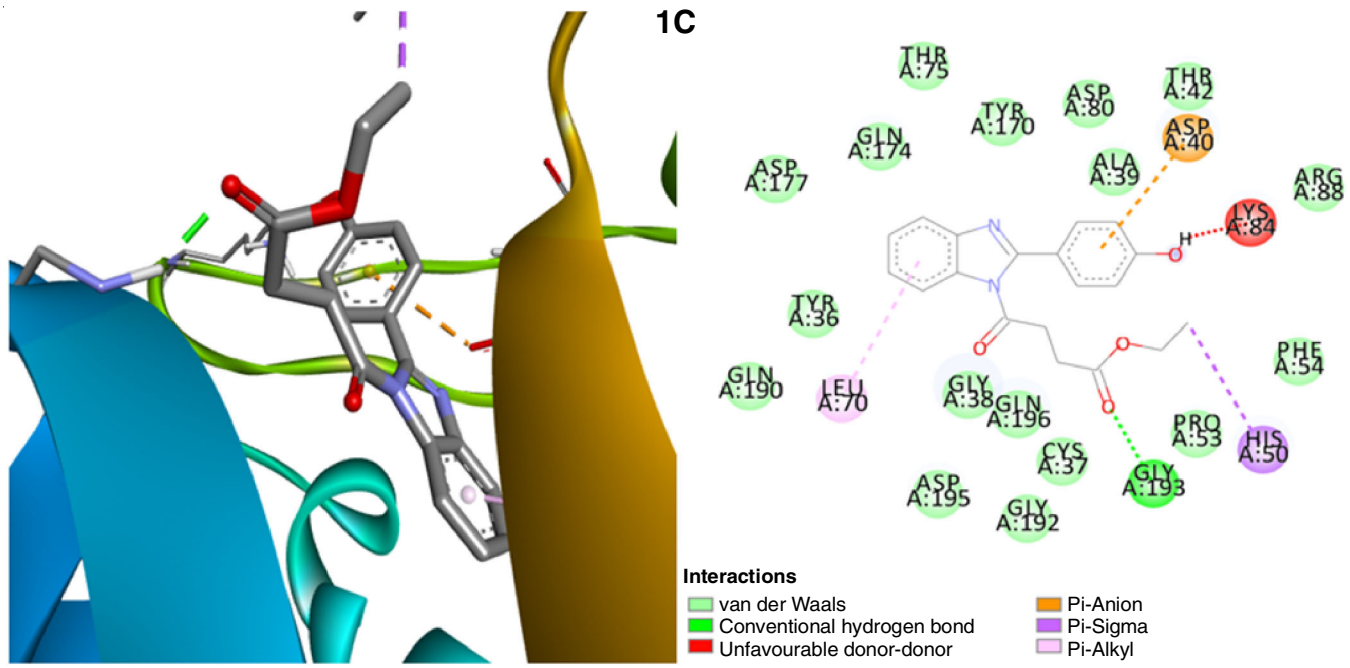
TABLE-1
MOLECULAR DOCKING SCORE OF STANDARD DRUG AND SYNTHESIZED SUBSTITUTED BENZIMIDAZOLES (**1C-14C**)

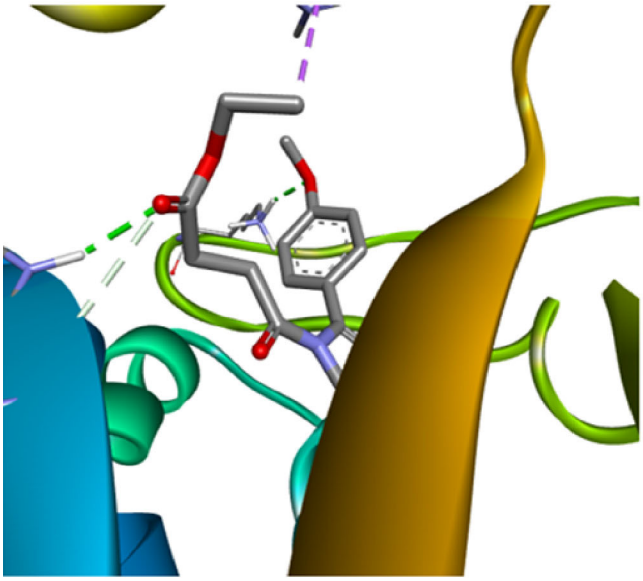
Compd.	Binding affinity (Kcal/mol)	Interacting residues	Residue involved conventional H-bond
1C	-8.9	Asp A:40, Lys A:84, His A:50, Gly A:193, Leu A:70	Gly A:193
2C	-8.9	His A:50, Gly A:193, Lys A:84, Gly A:192	Gly A:193, Lys A:84
3C	-8.8	Asp A:40, Asp A:80, Tyr A:170, Gln A:174, Thr A:75, Val A:191, Gln A:190, Gln A:196, Cys A:37, Asp A:195	Tyr A:170, Gln A:174
4C	-8.7	Asp A:40, Ala A:39, His A:50, Gly A:193, Leu A:70	Gly A:193
5C	-6.6	Asp A:40, Leu A:70	–
6C	-8.1	Asp A:40, Ala A:39, His A:50, Gly A:193	Asp A:40, Gly A:193
7C	-8.7	Asp A:40, Ala A:39, Gly A:193, Gln A:196, Leu A:70	Gln A:196
8C	-9.1	Asp A:40, His A:50, Gly A:193, Leu A:70, Tyr A:36	Gly A:193
9C	-9.2	Asp A:40, Lys A:84, His A:50, Gly A:193, Leu A:70, Tyr A:36, Arg A:88	Gly A:193, Lys A:84, Arg A:88
10C	-8.9	Asp A:40, Lys A:84, His A:50, Gly A:193, Leu A:70, Tyr A:36	Gly A:193, Lys A:84
11C	-8.9	Asp A:40, Leu A:70, Tyr A:36	–
12C	-6.9	Asp A:40, Lys A:84, His A:50	–
13C	-7.6	His A:50, Asp A:195, Pro A:53, Gly A:38, Gly A:193, Ala A:39	Gly A:193, His A:50
14C	-8.6	Asp A:40, Leu A:70, Tyr A:36	–
Pefloxacin (Standard)	-8.2	Asp A:195, His A:50, Pro A:53, Gly A:192, Gly A:193	Gly A:192, Gly A:193

dazoles, except three compounds (**5C**, **6C** and **13C**), has a higher binding affinity than the reference medication which is -8.2 Kcal/mol. Pefloxacin's binding residues include Asp A:195, His A:50, Pro A:53, Gly A:192 and Gly A:193, which form traditional hydrogen bonds with two amino acids (A:192 and A:193 Gly). In docking scores, these drugs performed better than the most common medication available. The best-docked ligands (**1C**, **2C**, **8C**, **9C**, **10C**, **11C**) and pefloxacin with their 3D binding surfaces and 2D ligand interactions are shown in Fig. 1. The results of molecular docking indicate that the heterocyclic benzimidazole compounds that have been chosen may have significant antibacterial action. To bacterial Topoisomerase-II enzyme inhibition, the chosen protein data bank (PDB Id: 1JIJ) may be a suitable target protein for benzimidazole derivatives to show their antibacterial activity. It appears from the docking studies that more structural alterations are needed in molecules **5C**, **6C** and **13C** to increase their potency against bacterial cells.

Conclusion

A series of fourteen 1,2-disubstituted benzimidazole derivatives were designed and synthesized by condensing 2-(2,3,4-substituted)benzimidazoles with ethyl succinyl chloride. Molecular docking studies were caried out for all the synthetic compounds against Topoisomerase-II enzyme and 11 compounds were identified as promising inhibitors. These compounds demonstrated robust binding with the target protein *via* hydrophobic and hydrogen bond interactions. The results revealed





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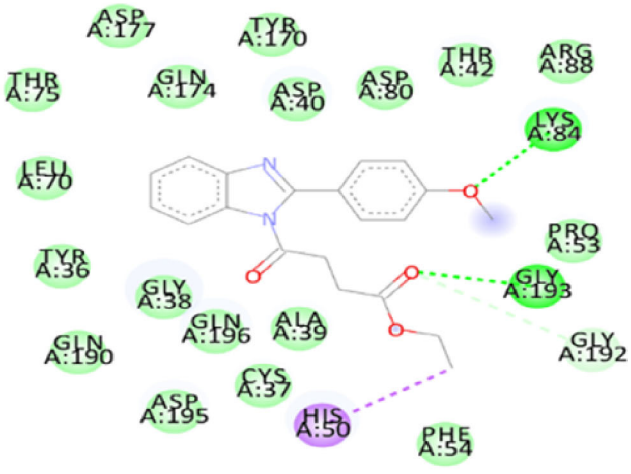
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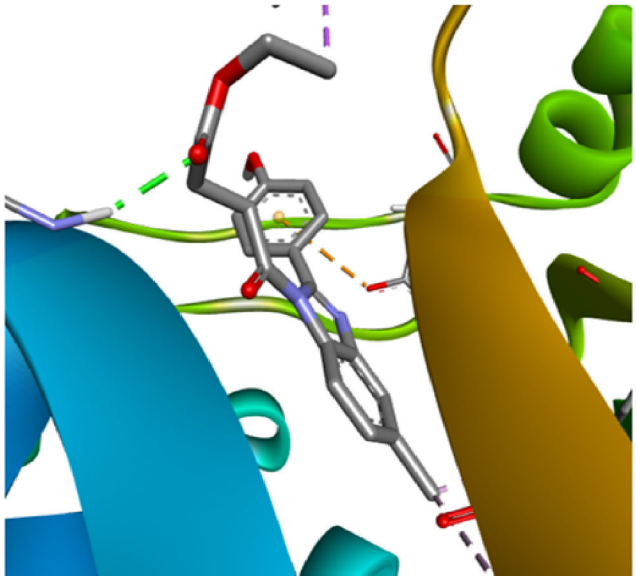
HIS A:50
PHE A:54
Interactions
van der Waals
Conventional hydrogen bond
Carbon hydrogen bond
Pi-Sigma



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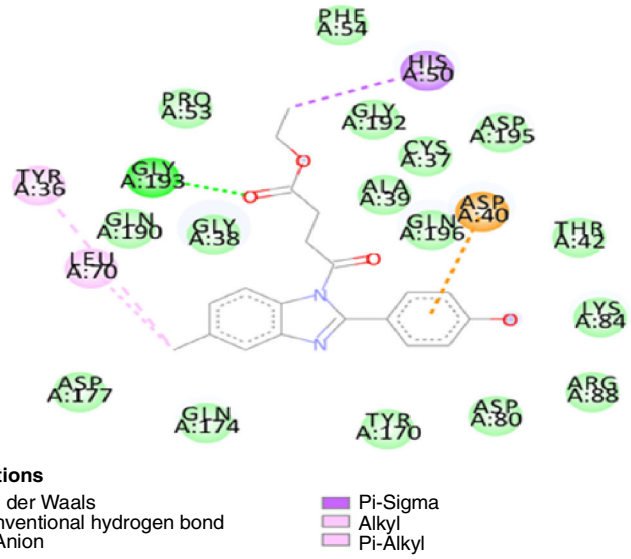
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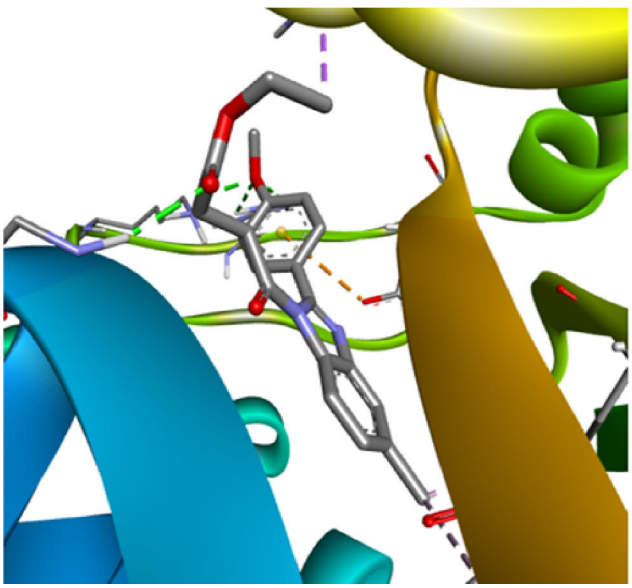

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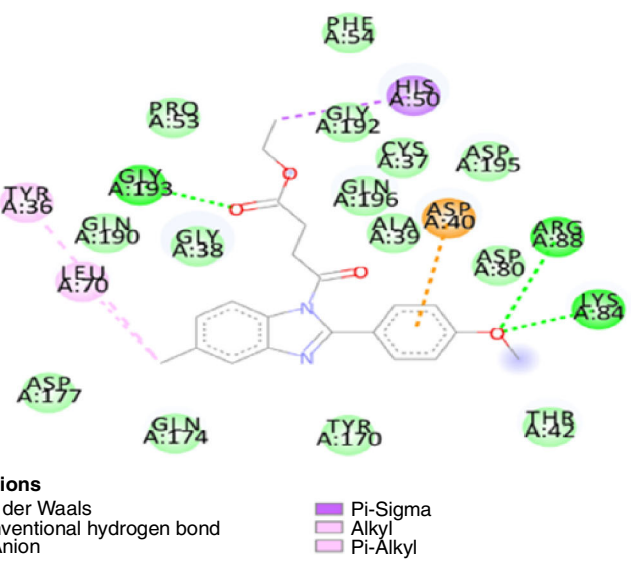
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TYR A:170
THR A:42
Interactions
van der Waals
Conventional hydrogen bond
Pi-Anion
Pi-Sigma
Alkyl
Pi-Alkyl

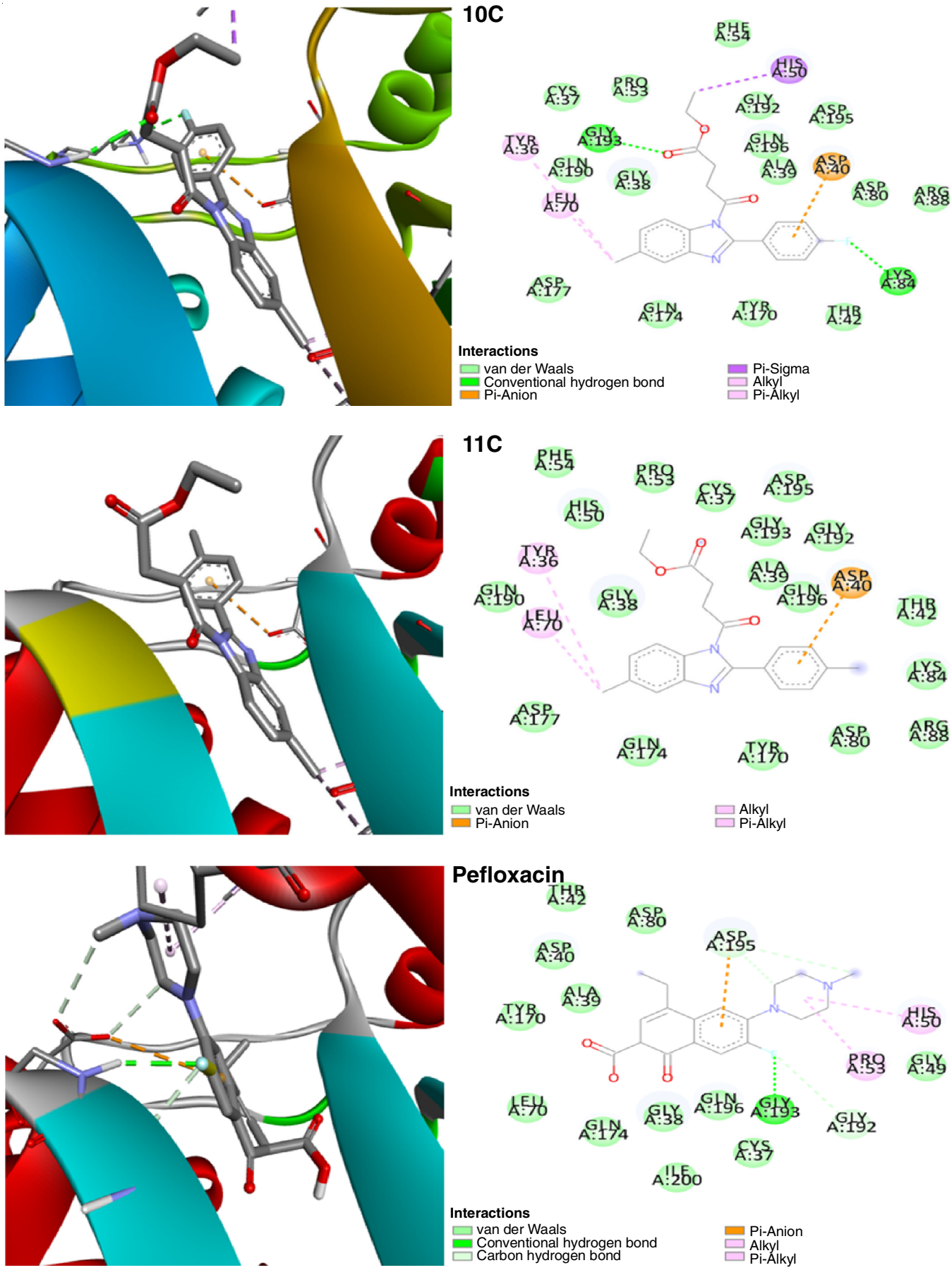

Fig. 1. 3D binding surface and 2D interaction diagram of compound **1C**, **2C**, **8C**, **9C**, **10C**, **11C** and pefloxacin with 1JIJ

that maximum synthetic compounds (except compounds **5C**, **6C** and **13C**) exhibited a greater propensity for binding when compared to pefloxacin. Thus, the newly synthesized benzimidazoles demonstrate potential as a novel class of antimicrobial agents and with further research, may evolve into the effective antibacterial drugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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